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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,875	03/22/2002	Midori Shima	2462-132US	8702

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Richard C Woodbridge
Woodbridge & Associates
PO Box 592
Princeton, NJ 08542-0592

EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,875	SHIMA ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-18 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-18 and 20* is/are rejected.

7)☒ Claim(s) *17,18 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0804*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

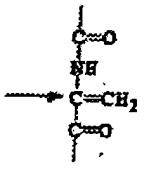
A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission, filed on August 2, 2004, has been entered. It is acknowledged that applicants have cancelled Claims 1-13 and 19, amended Claims 14-18, and added new Claim 20. Claims 14-18 and 20 are pending and are hereby considered.

Specification-Objections

The title is objected to. The title should be amended to reflect the instant invention, which are methods of treatment.

The Abstract is objected to for reciting "...an agent for curing disseminated intravascular coagulation". The specification fails to describe an agent for curing disseminated intravascular coagulation and the state of the art teaches that there is currently no cure for disseminated intravascular coagulation (Franchini et al, 2004). It is suggested that "curing" be amended to "treating".

The specification is objected to for providing two, conflicting definitions for the chemical state of anhydridized thrombin. The formula on page 8 presents the anhydridized residue of thrombin as dehydroalanine, comprising a carbon-carbon double bond at the α position:



Anhydridized FIIa

While, on page 11, lines 5-8, the specification states "In the 2nd step and 3rd step...transforming a serine residue to an alanine residue thereby producing an anhydridized serine protease...", indicating that the α carbon has a single bond: C-CH_3.

Clarification is required.

The specification is objected to for containing typographical and grammatical errors. The examples listed below are not meant to be exhaustive. The specification should be carefully check for errors.

For example:

page 1, line 7: "...the substrate f the serine protease..."

page 3, line 23: "An agent resisting digestive enzyme..."

page 8, line 3: "...powdery or sold state..."

page 10, line 28 and page 11, line 20: "...Mg^2..."

page 20, lines 1, 15, 17, 18, and 21,: "...tris..."

page 20, line 20: "...was dded to..."

page 21, last line: "...NalCL..."

page 22, line 17-18: "...capable of the exclusive selectively inhibiting exclusively..."

page 22, line 19-20: "it is not only useful as a thrombosis preventive of a new mechanism but also usable efficiently...".

Claims-Objections

The claim set is objected to for failing to begin as a sentence of which the claims are an object; for example, –We claim– or –The claims are–.

Claims 17 and 18 are objected to for the phrase "...in the presence of at least one of polyhydric alcohols or saccharides", which would be clearer if recited (as stated in the specification, page 8, line 17-18) as "...in the presence of at least one compound selected from the group consisting of polyhydric alcohols and saccharides".

Claim 20 is objected to for lacking an article in the phrase "...in patient in need...".

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification fails to define the phrase "resisting a digestive enzyme". Is Applicant's intention to recite a method for inhibiting a digestive enzyme or does "resisting" encompass some other intended meaning? The specification also fails to define "digestive enzyme". Is Applicant's intention to recite, based on the standard definition*, a method of inhibiting a digestive enzyme from the alimentary tract or is this term intended to be broader i.e. a method of inhibiting any hydrolase? Because the subject matter of the recited invention is unclear, Claim 20 is rejected under 35 U.S.C. 112, second paragraph.

> *Steadman's Medical Dictionary: *digestive*: relating to digestion; *digestion*: the process of making a digest; *digest*: to hydrolyze or break up by means of hydrolyzing enzymes, as in the action of the secretion of the alimentary tract upon food.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

In this regard, the application disclosure and claims are compared per the factors indicating in the decision re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These

factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 14, 15, 17, 18, and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating disseminated vascular coagulation using anhydridized blood coagulating factor II, anhydridized blood coagulating factor VIII, anhydridized blood coagulating factor IX, or anhydridized blood coagulating factor X, wherein anhydridization is at the active-site serine residue, the specification does not reasonably provide enablement for methods of treating disseminated vascular coagulation using any anhydridized serine protease which is capable of inhibiting the reaction of any serine protease by competitively binding the substrate of any said serine protease. In addition the specification is not enabling for any method for resisting a digestive enzyme in a patient in need of such treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 14, 17, and 18 are so broad as to encompass a method of treating disseminated vascular coagulation using any anhydridized serine protease that is capable of inhibiting the

reaction of any serine protease by competitively binding the substrate of any said serine protease. Claim 15 is so broad as to encompass a method of treating disseminated vascular coagulation using anhydridized blood coagulating factor II, anhydridized blood coagulating factor VIII, anhydridized blood coagulating factor IX, or anhydridized blood coagulating factor X wherein anhydridization is at any site and the anhydridized factor is capable of inhibiting the reaction of any serine protease by competitively binding the substrate of any said serine protease. Claim 20 is so broad as to encompass any method for resisting a digestive enzyme in a patient in need of such treatment comprising administering any anhydridized serine protease that is capable of inhibiting the reaction of any serine protease by competitively binding the substrate of any said serine protease. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to an extremely large number of methods of treatment using an extremely large number of serine protease inhibitors, as broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which proteins have the desired activity, which amino acids in the protease's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins's structure relates to its function. However, in this case the disclosure is limited to methods of treating disseminated vascular coagulation using anhydridized blood coagulating factor II, anhydridized blood coagulating factor VIII, anhydridized blood coagulating factor IX, and anhydridized blood coagulating factor X, wherein anhydridization is at the active-site serine residue.

While recombinant, mutagenic, and anhydridization techniques as well as methods for testing the anti-coagulation activity of compounds are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or anhydridizations.

The specification does not support the broad scope of Claim 14, 17, and 18, which encompasses any method for treating disseminated vascular coagulation using any anhydridized serine protease that competes with a serine protease for binding to a substrate. The specification does not support the broad scope of Claim 15, which encompasses treatment of disseminated vascular coagulation using any anhydridized blood coagulating factor II, anhydridized blood coagulating factor VIII, anhydridized blood coagulating factor IX, or anhydridized blood coagulating factor X. The specification does not support Claim 20, which encompasses a method for resisting a digestive enzyme in any patient by administering any anhydridized serine protease that competes with a serine protease for binding to a substrate.

The specification does not support the broad scope of Claims 14, 15, 17, 18, and 20 because the specification does not establish: (A) the structure of all anhydridized serine proteases that function by competing with a serine protease for binding to a substrate and can be used to treat disseminated vascular coagulation or provide resistance to a digestive enzyme; (B) the residues of any serine protease that can be anhydridized to produce an anhydridized serine

protease that functions by competing with a serine protease for binding to a substrate and can be used to treat disseminated vascular coagulation or provide resistance to a digestive enzyme; (C) regions of any anhydridized serine protease's structure which may be modified without effecting the function of being a serine protease inhibitor and being useful for treatment of disseminated vascular coagulation or providing resistance to a digestive enzyme; (D) the general tolerance of the function of any anhydridized serine protease inhibitor to modification and extent of such tolerance; (E) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful in treatment of disseminated vascular coagulation or providing resistance to a digestive enzyme; and (G) how to identify any patient in need of being treated by a method for resisting a digestive enzyme.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of methods for treating disseminated vascular coagulation or providing resistance to a digestive enzyme using any number of anhydridized serine proteases. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 14, 15, 17, 18, and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of methods for treating disseminated vascular coagulation or providing resistance to a digestive enzyme using anhydridized serine proteases. The specification teaches methods for treating disseminated vascular coagulation using only four representative species of such anhydridized serine proteases. The specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a method of treatment for disseminated vascular coagulation using an anhydridized serine protease. Moreover, the specification fails to disclose any method for resisting a digestive enzyme or patients in need of said method and, therefore, recitation of said method in Claim 20 is considered to be New Matter. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102 and 103

In view of the fact that it is unclear, for the anhydridized serine protease, whether the original, active-site serine residue is converted to dehydroalanine (with the α carbon of the residue having a double bond) or the original, active-site serine residue is converted to alanine

(with the α carbon of the residue having a single bond), as discussed above, both of the following rejections over the prior art are made.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolf et al, 1994 or Berkner et al, 1992. Wolf et al teach treatment of disseminated intravascular coagulation (col 8, lines 15-18) using a variant of Factor X in which the active-site serine residue has been converted to an alanine residue (Fig 3). Berkner et al teach treatment of disseminated intravascular coagulation (pg 15, lines 35-37) using a variant of Factor VII in which the active-site serine residue has been converted to an alanine residue (pg 8, lines 27-28). Therefore, Claims 14-18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolf et al, 1994 or Berkner et al, 1992.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf et al, 1994 or Berkner et al, 1992 in view of Ashton et al, 1995 and further in view of Levi, 2001. The

teachings of Wolf et al and Berkner et al are described above. Neither Wolf et al nor Berkner et al teach treatment of disseminated intravascular coagulation using a anhydridized serine protease wherein the original, active-site serine residue has been converted to dehydroalanine. Ashton et al teach anhydrothrombin in which the original, active-site serine residue is converted to dehydroalanine, wherein said anydrothrombin is enzymatically inactive (pg 6455, parg 3, lines 8-15; Fig 1). It would have been obvious to a person of ordinary skill in the art to use the anhydrothrombin of Ashton et al to treat disseminated intravascular coagulation. To do so is suggested by Wolf et al wherein they state that modified blood factors, which lack protease activity, can be used to interfere with the ability of endogenous factors to activate the clotting cascade and, thus can be used for the prevention or treatment of thrombosis (col 1, parg 1). Motivation to use the anhydrothrombin of Ashton et al to treat disseminated vascular coagulation derives from the desire to reduce mortality, for example, in septic patients (Levi, pg 167, Abstract). Motivation is also provided by the fact that the anhydrothrombin of Ashton et al can be produced by chemical means using commercially available thrombin and does not require sophisticated molecular biological techniques, which would be an advantage in less developed countries. The expectation of success is high as, treatment of disseminated vascular coagulation with blood factors, wherein the active-site serine is derivatized, is known in the art (Wolf et al and Beckner et al). Therefore, Claims 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf et al, 1994 or Berkner et al, 1992 in view of Ashton et al, 1995 and further in view of Levi, 2001.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.

AU 1652